Incidentally, a nucleic acid probe with modified DNA, such as 2'-o-methyloligoribonucleotide, inserted in an oligodeoxynucleotide is used primarily for the determination of RNA. Upon determination of RNA by the probe, it is preferred to subject an RNA solution as a sample to heat treatment at 80 to 100°C, preferably 90 to 100°C, most preferably 93 to 97°C for 1 to 15 minutes, preferably 2 to 10 minutes, most preferably 3 to 7 minutes before hybridization with the probe such that the higher-order structure of RNA can be degraded. Where the base strand of the nucleic acid probe is formed of 35 or fewer bases, addition of a helper probe, for example, an oligonucleotide the base sequence of which is (5')AGGCCGGCCCTTGACTTTCCT(3') (SEQ ID NO. 1) to a reaction mixture is preferred for raising the efficiency of the hybridization to the sequence region. In this case, the helper probe can be in an oligodeoxyribonucleotide form or in a 2'-o-methyloligoribonucleotide form. When a nucleic acid probe longer than a 35-base strand is used, however, it is only necessary to thermally denature target RNA. When the nucleic acid probe according to the present invention is hybridized to RNA as described above, the fluorescence intensity decreases corresponding to the concentration of RNA in the reaction mixture, and RNA can be determined to a final RNA concentration of about 1.50 pM.

Please replace the paragraph beginning on page 63, lines 9-14, with the following text:

Preparation of a nucleic acid probe to be hybridized to the base sequence of a nucleic acid ranging from the 335th base to 358th base counted from the 5' end in 16S rRNA of *Escherichia coli*, namely, preparation of a nucleic acid probe having a base sequence of (3')CCGCTCACGCATC(5') (SEQ ID NO. 2) was conducted as will be described hereinafter.

Please replace the paragraph beginning on page 63, line 16 to page 64, line 2, with the following text:

A deoxyribooligonucleotide, which had the base sequence of (3')CCGCTCACGCATC(5') (SEQ ID NO. 2) and contained $-(CH_2)_7-NH_2$ bonded to the OH group on the carbon atom at the 3' position of deoxyribose at the 3' end of the deoxyribooligonucleotide, was purchased from Midland Certified Reagent Company, U.S.A. From Molecular Probes, Inc., "FluoroReporter Kit F-6082" (trade name) was also purchased, which contained not only "BODIPY FL" propionic acid succinimidyl ester but also a reagent for conjugating the compound to the amine derivative of the oligonucleotide. The kit was caused to act on the above-purchased oligonucleotide, whereby a nucleic acid probe labeled with "BODIPY FL" was synthesized for use in this Example.

Please replace the paragraph beginning on page 66, line 15 to page 67, line 6, with the following text:

An oligonucleotide, which was to be hybridized to 23S rNA of *Escherichia coli* JM109, had a base sequence of (5') CCCACATCGTTTTGTCTGGG (3') (SEQ ID NO. 3) contained $-(CH_2)_7-NH_2$, bonded to the OH group on the carbon atom at the 3' position of the 5' end nucleotide of the oligonucleotide, was purchased from Midland Certified Reagent Company, U.S.A. as in Example 1. From Molecular Probes, Inc., "FluoroReporter Kit F-6082" (trade name) was also purchased, which contained not only "BODIPY FL" propionic acid succinimidyl ester but also a reagent for conjugating the compound to the amine derivative of the oligonucleotide. The kit was caused to act on the above-purchased oligonucleotide, whereby a nucleic acid probe labeled with "BODIPY FL" was synthesized. The synthesized product so obtained was purified as in Example 1, whereby the nucleic acid

probe labeled with "BODIPY FL" was obtained with a yield of 25% as calculated relative to 2 mM of the starting oligonucleotide.

Please replace the text on page 69, line 1, with the following text:

Name Target deoxyribooligonucleotide (SEQID NOS. 4-13)

Please replace the text on page 69, line 12, with the following text:

Name Invention probe (SEQ ID NOS. 14-20)

Please replace the text on page 72, line 1, with the following text:

Name Target deoxyribooligonucleotide (SEQ ID. NOS. 21-31)

Please replace the text on page 72, line 14, with the following text:

Name Invention probe (SEQ ID NOS. 32-42)

Please replace the text on page 74, line 3, with the following text:

Name Target deoxyribooligonucleotide (SEQ ID. NOS. 43-46)

Please replace the text on page 74, line 9, with the following text:

Name Invention probe (SEQ ID NOS. 47-50)

Please replace the paragraph beginning on page 77, line 8 to page 78, line 13 with the following text:

An oligonucleotide was purchased from Midland Certified Reagent Company, U.S.A. as in Example 1. The oligonucleotide had a base sequence of (5')CATCCCCACCTTCCTCCCAGTTGACCCCGGCAGTC(3') (SEQ ID. NO. 51) (35 base pairs) hybridizable specifically to the 16S rNA base sequence of KYM-7 strain, said base sequence being equivalent to the base sequence ranging from the 1156th base to the 1190th base of the 16S rRNA of *Escherichia coli* JM109, contained deoxyribonucleotides at the 1st to 16th bases and the 25th to 35th bases, respectively, said methyl-modified ribonucleotides

being modified with methyl groups at the OH group at the 2' position on the carbon atom or ribose, and was modified with $-(CH_2)_7-NH_2-$ at the phosphate group of the 5'-terminal group of the 35 base pairs. From Molecular Probes, Inc., "FluoroReporter Kit F-6082" (trade name) was also purchased, which contained not only "BODIPY FLC6" propionic acid succinimidyl ester but also a reagent for conjugating the compound to the amine derivative of the oligonucleotide. The kit was caused to act on the above oligonucleotide, whereby a nucleic acid probe labeled with "BODIPY FL/C6" was synthesized. The synthesized product so obtained was purified as in Example 1, whereby the nucleic acid probe labeled with "BODIPY FL/C6" was obtained with a yield of 23% as calculated relative to 2 mM of the starting oligonucleotide. This probe was named "35-nucleotides chained 2-O-Me probe".

Please replace the paragraph beginning on page 78, lines 14-21, with the following text:

Using a DNA synthesizer, a riboxyoligonucleotide having a base sequence of (5')AGGCCGGCCCTTGACTTTCCT(3') (SEQ ID NO. 52) was synthesized as in the above to provide it as a forward-type hepter probe. On the other hand, a riboxyoligonucleotide having a base sequence of (5')AUGGGAGUUCAGUAGUACCCGCAAUGCUGGUCC(3') (SEQ ID NO. 53) was synthesized by using a DNA synthesizer, thereby providing it as a reverse type helper probe.

Please replace the paragraph beginning on page 81, lines 12-15, with the following text:

9) A ribooligonucleotide having a sequence of (5')GUGACGGUCACUAUUUGACCUCCUUCCACCCC(3') (SEQ ID NO. 54) (35-base ribooligonucleotide).

Please replace the paragraph beginning on page 81, lines 16-18, with the following text:

10) A ribooligonucleotide having a base sequence of (5')GUGACGGUCACUAUUUG(3') (SEQ ID NO. 55) (17-base ribooligonucleotide).

Please replace the text on page 83, line 11, with the following text:

(5') CATCCCCACCTTCCTCCGAGTTGACCCCGGCAGTC(3') (SEQ ID NO. 56)

Please replace the text on page 83, line 15, with the following text:

(5') CATCCCCACCTTCCTCTCGGCTTATCACCGGCAGTC (3') (SEQ ID NO. 57)

Please replace the text on page 86, lines 3-8, with the following text:

Invention probe: 3'TTTTTTTTGGGGGGGGC5' BODIPY FL/C6 (SEQ ID NO. 58)

Target nucleotide No. 1: 5'AAAAAAAACCCCCCCCA3' (SEQ ID NO. 59)

Target nucleotide No. 2: 5'AAAAAAAACCCCCCCCC3' (SEQ ID NO. 60)

Target nucleotide No. 3 : 5'AAAAAAAACCCCCCCCCI3' (SEQ ID NO. 61)

(I: hypoxanthine)

Target nucleotide No. 4: 5"AAAAAAAACCCCCCCCCI3' (SEQ ID NO. 62)

Please replace the paragraph beginning on page 87, line 17 to page 88, line 18, with the following text:

A model of A DNA chip according to the present invention is illustrated in FIG. 6. Firstly, a modified probe and a surface-treated slide glass are provided first. The modified probe had been prepared by introducing an amino group onto the 3'-OH group at the 3' end of the invention probe, 3'TTTTTTTTGGGGGGGGC5' (SEQ ID NO. 63) BODIPY FL/C6, prepared in Example 13. On the other hand, the surface-treated slide glass had been prepared by treating a slide glass with a silane coupling agent which contained epoxy groups as

reactive groups. A solution with the modified probe contained therein was applied in spots onto the surface-treated slide glass by a DNA chip production apparatus, "GMS™ 417 ARRAYER" (manufactured by TAKARA SHUZO CO., LTD., Kyoto, Japan). As a result, the modified probe is bound at the 3' end onto a surface of the slide glass. The slide glass is then placed for 4 hours or so in a closed vessel to bring the reaction to completion. The slide glass was alternately dipped in 0.1% SDS solution and water, twice in each of the solution and water, fox about 1 minute each time. Further, the slide glass was immersed for about 5 minutes in a boron solution, which had been prepared by dissolving $NaBH_4$ (1.0 g) in water (300 mL). Shortly after the slide glass was placed for 2 minutes in water of 95 °C, the slide glass was alternately dipped in 0.1% SDS solution and water, twice in each of the solution and water, for about 1 minute each time, so that reagents were washed off. The slide glass was then dried. As a result, a DNA chip according to the present invention was prepared.

Please replace the paragraph beginning at page 89, line 20 to page 90, line 10, with the following text:

A deoxyribooligonucleotide having a base sequence of (5')CATCGTTTACGGCGTGGAC(3') (SEQ ID NO. 64) was synthesized using a DNA synthesizer, "ABI394" (trade name: manufactured by Perkin Elmer, Corp.). An oligonucleotide, which had been prepared by treating the phosphate group at the 5' end of the oligodeoxyribonucleotide with phosphatase to form cytosine and then bonding $-(CH_2)_9-NH_2$ to the OH group on the carbon atom at the 5'-position of the cytosine, was purchased from Midland Certified Reagent Company. From Molecular Probes, Inc., "FluoroReporter. Kit F-6082" (trade name) was also purchased, which contained not only "BODIPY FL" propionic acid succinimidyl ester but also a reagent for conjugating the compound to the amine

derivative of the oligonucleotide. The kit was caused to act on the above-purchased oligonucleotide, whereby Primer 1 of the present invention labeled with "BODIPY FL/C6" was synthesized.

Please replace the paragraph beginning on page 91, lines 9-14, with the following text:

Primer 2 composed of a deoxyribooligonucleotide, which had a base sequence of (5')CCAGCAGCCGCGGTAATAC(3') (SEQ ID NO. 65), and a fluorescent dye ("BODIPY FL/C6") labeled to the 5' end of the deoxyribooligonucleotide, was prepared with a yield of 50% in a similar manner as in Example 13.

Please replace the text beginning on page 95, lines 4-6, with the following text:

- Forward primer E8F: (3')AGAGTTTGATCCTGGCTCAG(5') (SEQ ID NO. 66)

- Reverse primer E1492R: GGTTACCTTGTTACGACTT(5') (SEQ ID NO. 67)

c) Probe: BODIPY FL- (3') CCTTCCCACATCGTTT (5') (SEQ ID NO. 68)

Please replace the paragraph beginning on page 97, lines 1-17, with the following text:

A deoxyribooligonucleotide having a base sequence of (5')CTGGTCTCCTTAAACCTGTCTTG(3') (SEQ ID NO. 69)was synthesized using a DNA synthesizer, "ABI394" (trade name; manufactured by Perkin Elmer, Corp.). An oligonucleotide, which had been prepared by treating the phosphate group at the 5' end of the oligodeoxyribonucleotide with phosphatase to form cytosine and then bonding $-(CH_2)_9-NH_2$ to the OH group on the carbon atom at the 5'-position of the cytosine, was purchased from Midland Certified Reagent Company. From Molecular Probes, Inc., "FluoroReporter Kit F-6082" (trade name) was also purchased, which contained not only "BODIPY FL" propionic

acid succinimidyl ester but also a reagent for conjugating the compound to the amine derivative of the oligonucleotide. The kit was caused to act on the above-purchased oligonucleotide, whereby Primer KM38+C of the present invention labeled with "BODIPY FL/C6" was. synthesized.

Please replace the paragraph beginning on page 98, lines 16-18, with the following text:

A deoxyribooligonucleotide having a base sequence of (5')GGTTGGCCAATCTACTCCCAGG(3') (SEQ ID NO. 70) was synthesized in a similar manner as in Example 18.

Page 123 (Abstract), after the last line, beginning on a new page, please insert the attached Sequence Listing.

IN THE CLAIMS

Please amend the claims as follows:

Please cancel Claims 1, 12-14, 16-20, 22 and 27-45.

2. (Twice Amended) A nucleic acid probe for determining a concentration of a target nucleic acid, said probe being labeled with a fluorescent dye, wherein:

said probe is labeled at an end portion thereof with said fluorescent dye, and

said probe has a base sequence designed such that, when said probe is hybridized with said target nucleic acid, at least one G (guanine) base exists in a base sequence of said target nucleic acid at a position 1 to 3 bases apart from an end base portion where said probe and said target nucleic acid are hybridized with each other;